

## Rh-Catalyzed one-pot and practical transformation of aldoximes to amides

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**Wilkinson's complex has been found to catalyze the one-pot transformation of aldoximes to the corresponding amides with high selectivity and efficiency under essentially neutral conditions.**

Studies on organic transformations of certain functional groups into more useful moieties have been recently accelerated mainly due to the development of transition metal catalysts with advanced properties.<sup>1</sup> Among these, the inter-conversion of carbonyl groups and their equivalents is one of the most important processes in organic synthesis. Although numerous reagents have been introduced for these reactions,<sup>2</sup> efforts aimed at developing more efficient and practical catalytic systems are still actively underway for various reasons including economic and environmental. During our studies on metal-catalyzed reactions,<sup>3</sup> we have recently reported that aldoximes can be readily dehydrated under mild conditions to afford nitriles using a Ru catalyst (Scheme 1, eqn. 1).<sup>4</sup> Based on this result, we have tried to find a new catalytic system for the subsequent conversion of nitrile to amide. Instead of the plausible two-step sequence, however, we have found that a net transformation of aldoximes to the corresponding amides can be readily achieved in one-pot† by rhodium catalysis with high selectivity and efficiency (Scheme 1, eqn. 2), which is described in this communication.<sup>5</sup>





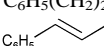
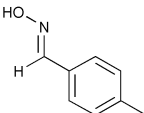
We first investigated the catalytic activities of a diverse range of metal complexes for the transformation of benzaldoxime. Although some metal catalysts showed measurable activities for conversion of the aldoxime to the corresponding nitrile under certain conditions, subsequent *in situ* catalytic hydrolysis of nitrile adduct turned out to be more difficult to perform.<sup>7</sup> For example, when benzaldoxime was treated with [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> catalyst (5 mol%) in DMF over 4 h at 150 °C, conversion was incomplete (53%) in the absence of any additives such as molecular sieves, and the ratio of formed benzonitrile to benzamide was determined to be 1 : 2. Other ruthenium catalysts examined displayed rather lower activities or decreased selectivities under the same conditions: RuH<sub>2</sub>(PPh<sub>3</sub>)<sub>4</sub> (77% conversion, 1 : 1),<sup>6</sup> Ru<sub>3</sub>(CO)<sub>12</sub> (19% conversion, 3 : 1), and RuCl<sub>3</sub> (67% conversion, 1 : 1). In contrast, rhodium catalysts exhibited enhanced selectivity for the generation of benzamide compared to the ruthenium complexes.

Some examples are: [Rh(OAc)<sub>2</sub>]<sub>2</sub> (in DMF, 150 °C, 4 h, 88% conversion, nitrile : amide, 1 : 4), [RhCl(cod)]<sub>2</sub> (67%, 1 : 4), [(PPh<sub>3</sub>)<sub>3</sub>Rh(nbd)]<sup>+</sup>PF<sub>6</sub><sup>-</sup> (77%, 1 : 6), and RhCl(PPh<sub>3</sub>)<sub>3</sub> (92%, 1

: 6).<sup>8</sup> The catalytic activity and selectivity of the Wilkinson catalyst was slightly improved when the reaction was carried out in toluene under otherwise identical conditions (>95% conversion, nitrile : amide, 1 : >9). When the reaction was carried out at lower temperatures, benzamide was obtained in lower yields due to slower conversion: 89% (150 °C, 4 h), 57% (130 °C), and 43% yield (110 °C).<sup>9</sup>

Next, we investigated the scope and generality of the above RhCl(PPh<sub>3</sub>)<sub>3</sub>-catalyzed conversion of aldoximes to amides (see Table 1). Aldoximes used in this study were quantitatively prepared from the reaction of the corresponding aldehydes with hydroxylamine hydrochloride. Aldoximes were used as a mixture of *Z*- and *E*-isomers though in most cases the *E*-form is the major isomer. Benzaldoximes with substituents of varying electronic properties were all smoothly converted to the corresponding amides in high yields (entries 1–6) and only negligible amounts of nitriles were obtained. Regardless of the electronic properties of substituents on aldoximes, the reaction resulted in high efficiency and selectivity. Several functional groups including ester moieties were tolerated under the

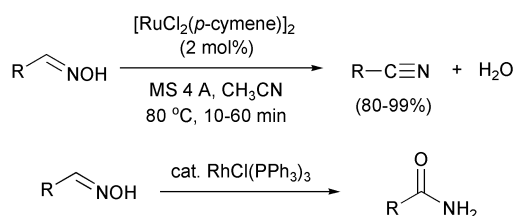
**Table 1** Rh-Catalyzed one-pot conversion of aldoximes to amides<sup>a</sup>

Entry	R	Solvent	t/h	Yield (%) <sup>b</sup>
1	C <sub>6</sub> H <sub>5</sub>	Toluene	2	89
2	(4-Br)C <sub>6</sub> H <sub>4</sub>	Toluene	2	78
3	(4-NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub>	Toluene	2	78
4	(4-BnO)C <sub>6</sub> H <sub>4</sub>	Toluene	4	80
5	(4-BnO <sub>2</sub> C)C <sub>6</sub> H <sub>4</sub>	Toluene	4	85
6	(2,6-Cl)C <sub>6</sub> H <sub>3</sub>	DMF	5	73
7		DMF	2	80
8		Toluene	5	93
9		DMF	5	84
10		DMF	5	74
11	Cyclohexyl	Toluene	5	87
12	C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub>	Toluene	5	98
13		Toluene	5	94
14		DMF	4	94 <sup>c</sup>

<sup>a</sup> See the Notes and references† for a typical experimental procedure.

<sup>b</sup> Isolated yields after crystallization or chromatography on silica gel.

<sup>c</sup> Yield of isolated bisamide (1,4-benzenedicarboxamide) starting from 1,4-bisaldoxime.



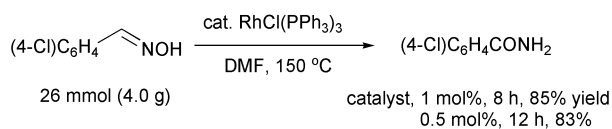
**Scheme 1** Selective conversion of aldoximes to nitriles or amides.

conditions (entry 5). Sterically congested aldoximes such as 2,6-dichlorobenzaldoxime were also readily converted to the corresponding amide in good yield (entry 6).

The presence of heteroatoms including S, O, and N in the substrates did not alter the efficiency or selectivity, and a range of heteroaromatic amides were obtained in good yields (entries 7–10). It should be mentioned that *syn*-aldoximes react faster than the corresponding *anti*-isomer, and enrichment of the *anti*-isomer in the early stages was observed. For example, when 2-thiophene-*syn*-aldoxime<sup>10</sup> was allowed to react, 80% conversion was observed over 30 min (toluene, 130 °C, 1 mol% Wilkinson catalyst). In contrast, conversion of the *anti*-isomer was much lower (19%) and isomerization to the *syn*-aldoxime was observed to occur to some extent. Not only aromatic but also aliphatic aldoximes could be employed as facile substrates for the transformation (entries 11–12). Whereas toluene was used as a facile solvent in general, DMF turned out to be more suitable for substrates of poor solubility such as pyridyl-containing aldoximes (entries 9–10). A conjugated aldoxime such as *trans*-cinnamaldehyde oxime was also readily converted to the conjugated amide (entry 13). As shown in entry 14, when a substrate bearing a bisaldoxime group was treated with the rhodium catalyst, a satisfactory yield of the corresponding bisamide was obtained.

Although the exact pathway of the Rh-catalyzed transformation is not clear at the present stage, two plausible scenarios can be suggested on the basis of the experimental results. The first involves a nitrile intermediate. Formation of amides from aldoximes under the conditions used was accompanied by generation of nitriles as a by-product albeit in small amounts (< 8%) in most substrates examined. Moreover, the Rh complex catalyzes hydrolysis of benzonitrile to benzamide though the efficiency was lower (H<sub>2</sub>O 3 equiv., Rh 10 mol%, 150 °C, 12 h, toluene, 55% benzamide) compared to that under the one-pot conditions. The fact that ketoximes and *O*-alkyl aldoximes were intact under the conditions would be additional indirect evidence for the nitrile intermediacy. Another possible route, a direct rearrangement of aldoximes to nitriles by action of the rhodium catalyst, can also be envisaged to operate either exclusively or in parallel with the above stepwise pathway.<sup>11</sup> When the reaction was carried out in the presence of water (3 equiv. to aldoxime), the reaction rate and selectivity were little changed compared to those of the anhydrous conditions. The fact that even when water scavenger such as MS (4 Å, 3 equiv. to benzaldoxime) was added, amide was still produced albeit in lower yield (52%, 48 h, 150 °C) would be an additional outcome favoring the direct rearrangement pathway. Dehydration of amides to the corresponding nitrile precursors was not catalyzed by the Ru or Rh complexes examined.<sup>12</sup>

The adaptability of the present catalytic system to a large-scale process was next examined. Complete conversion of 4-chlorobenzaldehyde oxime (26 mmol, 4.0 g) was achieved with as low as 0.5 mol% of RhCl(PPh<sub>3</sub>)<sub>3</sub> catalyst within 12 h affording 4-chlorobenzamide in good yield (Scheme 2).



Scheme 2

In summary, a highly efficient and selective catalytic protocol has been developed for the one-pot conversion of aldoximes to amides under essentially neutral conditions, which, to the best of our knowledge, has not been reported previously. The procedure is characterized to be atom-economical<sup>13</sup> and environmentally friendly<sup>14</sup> because the transformation occurs in the absence of any additives except for catalyst and it does not generate any by-products.

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## Notes and references

† Typical procedure for rhodium-catalyzed one-pot conversion of aldoximes to amides: To a solution of 4-bromobenzaldoxime (400.0 mg, 2.0 mmol) in toluene (0.5 mL) was added RhCl(PPh<sub>3</sub>)<sub>3</sub> (93 mg, 0.1 mmol), and the mixture was stirred for 2 h at 150 °C. After completion of the reaction, which was checked by TLC, analytically pure 4-bromobenzamide (312 mg, 78%) was obtained after recrystallization from diethyl ether.

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